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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,009	07/14/2006	Behrooz Sharifi	67789-516	6133

50670 7590 12/03/2009

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EXAMINER	
HILL, KEVIN KAI	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
12/03/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/564,009	SHARIFI ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7,8 and 11-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7,8 and 11-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 September 2009* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Amendments

Applicant's response and amendments, filed September 15, 2009, to the prior Office Action is acknowledged. Applicant has cancelled Claims 2, 6 and 9-10, amended Claims 1, 3, 5 and 7-8, and added new claims, Claims 11-14. Applicant's new claims have been entered into the application as requested and will be examined on the merits herein.

Claims 1, 3-5, 7-8 and 11-14 are under consideration.

Priority

This application is a 371 of PCT/US04/22827 filed July 15, 2004. Applicant's claim for the benefit of a prior-filed application parent provisional application 60/487,409, filed on July 15, 2003 under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the September 15, 2009 response will be addressed to the extent that they apply to current rejection(s).

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Drawings

1. **The Drawings filed September 15, 2009 are acceptable.** The Examiner acknowledges Applicant's petition in the papers filed September 15, 2009 to accept color drawings/photographs and amending the specification accordingly.

Claim Objections

2. **The prior objection to Claims 1 and 5 is withdrawn** in light of Applicant's amendment to the claims.

3. **Claim 13 is objected to under 37 CFR 1.75(c),** as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

In the instant case, the claim is drawn to an isolated endothelial cell produced by the method of transducing a monocytic cell *in vitro* with a retrovirus expressing PTN. Because the transdifferentiation necessarily occurs *in vitro*, as there is no step to remove the transduced monocytic cell from the *in vitro* environment during transdifferentiation, Claim 13 is redundant with and fails to further limit the isolated endothelial cells of Claim 5.

Correction and/or clarification is required.

4. **Claim 14 is objected to under 37 CFR 1.75(c),** as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

In the instant case, the claims are drawn to an isolated endothelial cell produced by the method of transducing a monocytic cell *in vitro* with a retrovirus expressing PTN. If the transdifferentiation occurs *in vivo*, as claimed, then the resulting endothelial cells are no longer "isolated". Thus, Claim 14 fails to further limit the **isolated** endothelial cells of Claim 5.

Correction and/or clarification is required.

Claim Rejections - 35 USC § 101

5. **The prior rejection of Claims 5-8 under 35 U.S.C. 101 is withdrawn** in light of Applicant's amendment to Claim 5 reciting "isolated" before "endothelial cell".

Claim Rejections - 35 USC § 112

6. **The prior rejection of Claims 1 and 5 under 35 U.S.C. 112, second paragraph, is withdrawn** in light of Applicant's amendment to the claims.

Claim Rejections - 35 USC § 112

7. **The prior rejection of Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, is withdrawn** in light of Applicant's amendment to the claims.

New matter

8. **Claim 14 is rejected under 35 U.S.C. 112 first paragraph,** as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention because the specification as originally filed does not describe the invention as now claimed. Claim 14, added by amendment on September 15, 2009, recites an isolated endothelial cell, whereby transdifferentiation of a monocytic cell into an endothelial cell occurs *in vivo*. Clear support for the isolation of an endothelial cell comprising a retrovirus expressing PTN that transdifferentiated *in vivo* from a monocytice cell cannot be found in the instant application or priority documents. Accordingly, Claim 14 is considered to constitute new matter.

> MPEP §2163.06 notes "IF NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2D 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "WHENEVER THE ISSUE ARISES, THE FUNDAMENTAL FACTUAL INQUIRY IS WHETHER A CLAIM DEFINES AN INVENTION THAT IS CLEARLY CONVEYED TO THOSE SKILLED IN THE ART AT THE TIME THE APPLICATION WAS FILED...IF A CLAIM IS AMENDED TO INCLUDE SUBJECT MATTER, LIMITATIONS, OR TERMINOLOGY NOT PRESENT IN THE APPLICATION AS FILED, INVOLVING A DEPARTURE FROM, ADDITION TO, OR DELETION FROM THE DISCLOSURE OF THE APPLICATION AS FILED, THE EXAMINER SHOULD CONCLUDE THAT THE CLAIMED SUBJECT MATTER IS NOT DESCRIBED IN THAT APPLICATION". MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. *Applicant should therefore specifically point out the support for any amendments made to the disclosure*" (emphasis added).

In the instant case, the specification as originally filed describes the transduction of RAW monocytic cells with a retrovirus expressing PTN. The transduced RAW cells were then transplanted into the chorioallantoic membrane (CAM) of quail embryos (pg 13) or injected via tail vein into a mouse hindlimb ischemia model (pg 15), whereby the PTN-expressing RAW cells appear to transdifferentiate into endothelial cells. However, the specification is silent regarding the subsequent isolation of said endothelial cells that were the *in vivo* transdifferentiated products of the PTN-expressing RAW cells. Thus, the amendment is a departure from or an addition to the disclosure of the application as filed.

Alternatively, if Applicant believes that support for Claim 14 drawn to the subsequent isolation of endothelial cells that are the *in vivo* transdifferentiated products of PTN-expressing monocytes, is present and clearly envisaged in the instant application or earlier filed priority documents, Applicant must, in responding to this Office Action, point out with particularity, where such support may be found.

Applicant does not indicate where these limitations are supported by the original specification, or how, as is Applicant's burden. See MPEP §714.02, last sentence of the third paragraph from the end and MPEP §2163.06 (I) last sentence.

Claim Rejections - 35 USC § 102

9. **The prior rejection of Claims 5-8 under 35 U.S.C. 102(b)** as being anticipated by Pavlov et al (Mol. Cell. Neurosci. 20(2):330-342, 2002), as evidenced by Hellstrom et al (Development 126(14):3047-3055, 1999; Abstract only) **is withdrawn** in light of Applicant's amendment to the claims, whereby the process steps introduce a structural limitation of the claimed cells to comprise a retrovirus expressing PTN, a limitation that Pavlov et al do not teach, which the Examiner finds persuasive.

10. **The prior rejection of Claims 5-8 under 35 U.S.C. 102(b)** as being anticipated by Abbot et al (Arth. Rheum. 35(4):401-406, 1992; Abstract only) as evidenced by Pufe et al (Arth. & Rheum. 48(3):660-667, 2003; *of record in IDS) **is withdrawn** in light of Applicant's amendment to the claims, whereby the process steps introduce a structural limitation of the

claimed cells to comprise a retrovirus expressing PTN, a limitation that Abbot et al do not teach, which the Examiner finds persuasive.

Claim Rejections - 35 USC § 103

11. **Claim 1 stands and Claim 11 is newly rejected under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (*of record) in view of Souttou et al (2001; *of record in IDS) and Powers et al (2002; *of record).

Determining the scope and contents of the prior art.

With respect to the steps of differentiating the monocytes into endothelial cells *in vitro*, Havemann et al disclose the isolated mononuclear cells are cultured and differentiated to give endothelial-like cells *in vitro* [0067, 0069].

Response to Arguments

Applicant argues that Havemann et al do not reasonably teach the use of PTN to obtain endothelial cells. The disclosure of PTN is in the context of a possible growth factor, selected from a list of at least 33 other growth factors, that can be used in the culture medium for mononuclear cells to influence differentiation, survival, migration and vascularization. There is no indication of which growth factor is responsible for differentiation of mononuclear cells into endothelial cells.

Applicant's argument(s) has been fully considered, but is not persuasive. The prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed. *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). In the instant case, Havemann et al clearly disclose PTN as a growth factor used in the step of culturing monocytes to differentiate into endothelial-like cells or endothelial progenitor cells.

Applicant argues that Havemann et al do not reasonably disclose a retroviral vector to transform a gene encoding a growth factor into the monocytic cells to promote the endothelialization of injured vessels or angiogenesis.

Applicant's argument(s) has been fully considered, but is not persuasive. The focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person would have reasonably expected to have been able to do in view of that knowledge. This is so regardless of whether the source of that knowledge and ability was documentary prior art, general knowledge in the art, or common sense. M.P.E.P. §2141.

The person of ordinary skill in the art is a hypothetical person who is presumed to have known the relevant art at the time of the invention. Factors that may be considered in determining the level of ordinary skill in the art may include: (1) "type of problems encountered in the art;" (2) "prior art solutions to those problems;" (3) "rapidity with which innovations are made;" (4) "sophistication of the technology; and" (5) "educational level of active workers in the field. In a given case, every factor may not be present, and one or more factors may predominate." *In re GPAC*, 57 F.3d 1573, 1579, 35 USPQ2d 1116, 1121 (Fed. Cir. 1995); *Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.,* 807 F.2d 955, 962, 1 USPQ2d 1196, 1201 (Fed. Cir. 1986); *Environmental Designs, Ltd. V. Union Oil Co.,* 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983).

It is proper to "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc*., 127 S. Ct. 1727, 1741,82 USPQ2d 1385, 1396 (2007). See also Id. At 1742, 82 USPQ2d 1397 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton."). Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See *CTS Com. v. Electro Materials Corp*. of America 202 USPQ 22 (DC SINY); and *In re Burckel* 201 USPQ 67 (CCPA).

Havemann et al do not disclose *ipsis verbis* that the viral vector to transfect the mononuclear cells to be a retroviral vector. However, Havemann et al disclose that the vector may be a viral vector [0049], and those of ordinary skill in the prior art recognized that retroviral vectors are routinely used to express a gene of interest [0002, 0004]. Based on the teachings in the art as a whole, one of ordinary skill in the art would have the common sense that a retroviral

vector is embraced by Havemann's disclosure of a "viral vector" to transform a gene encoding a growth factor into the monocytic cells.

Applicant argues that while Havemann et al allows for the possibility that the mononuclear cells are transfected with the nucleic acid construct for gene therapy, the rationale provided by the Examiner does not support the rejection under §103(a) because the results would not have been predictable to the ordinary artisan and there would not be a reasonable expectation of success. The Examiner has not shown that the ordinary artisan would find that using a monocytic cell transduced with a retrovirus expressing PTN would predictably transdifferentiate into an endothelial cell. Havemann et al made no indication of which growth factor is responsible for differentiation of the mononuclear cells into endothelial cells.

Applicant's argument(s) has been fully considered, but is not persuasive. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Havemann et al clearly disclose PTN as a growth factor used in the step of culturing monocytes to differentiate into endothelial-like cells or endothelial progenitor cells. Souttou et al taught that PTN is an angiogenic factor acting on endothelial cell proliferation, migration, survival, and capillary-like structure formation (pg 64, col. 1, last ¶). The prior art recognized that PTN has autocrine and paracrine stimulatory activities in cells expressing both PTN and the PTN receptor (Powers et al, pg 14155, col. 1, ¶4). While Havemann et al do not teach *ipsis verbis* that the mononuclear cells/monocytes express the PTN receptor, those of ordinary skill in the art would reasonably understand that the PTN receptor is necessarily present because the mononuclear cells/monocytes are disclosed to respond to PTN to give rise to endothelial cells. Thus, the expression of an effector transgene in the mononuclear cells [which includes monocytes] (Havemann) encoding PTN (Souttou) would be reasonably expected to achieve autocrine and paracrine stimulatory activities (Powers), promoting the differentiation of the mononuclear cells into endothelial cells (Havemann).

Applicant argues that the Examiner has not shown that the ordinary artisan would believe that there is a reasonable expectation of success in using a monocytic cell transduced with a retrovirus expressing PTN to effect the gene therapy method contemplated by Havemann et al.

Applicant's argument(s) has been fully considered, but is not persuasive. In response to Applicant's argument that the references fail to show certain features of Applicant's invention, it is noted that the features upon which Applicant relies (i.e., the gene therapy method contemplated by Havemann et al) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In the instant case, the claims are drawn to a method of transdifferentiating a monocytic cell into an endothelial cell, and the isolated endothelial cell made by said method. Havemann et al clearly disclose PTN as a growth factor used in the step of culturing monocytes to differentiate into endothelial-like cells or endothelial progenitor cells. Souttou et al taught that PTN is an angiogenic factor acting on endothelial cell proliferation, migration, survival, and capillary-like structure formation (pg 64, col. 1, last ¶). The prior art recognized that PTN has autocrine and paracrine stimulatory activities in cells expressing both PTN and the PTN receptor (Powers et al, pg 14155, col. 1, ¶4). While Havemann et al do not teach *ipsis verbis* that the mononuclear cells/monocytes express the PTN receptor, those of ordinary skill in the art would reasonably understand that the PTN receptor is necessarily present because the mononuclear cells/monocytes are disclosed to respond to PTN to give rise to endothelial cells. Thus, the expression of an effector transgene in the mononuclear cells [which includes monocytes] (Havemann) encoding PTN (Souttou) would be reasonably expected to achieve autocrine and paracrine stimulatory activities (Powers), promoting the differentiation of the mononuclear cells into endothelial cells (Havemann).

Applicant argues that the Examiner has exercised impermissible hindsight in order to reject the claims.

Applicant's argument(s) has been fully considered, but is not persuasive. In response to Applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense

necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, the Examiner has taken into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made.

12. **Claim 3 stands rejected under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (*of record) in view of Souttou et al (2001; *of record in IDS) and Powers et al (J2002; *of record), as applied to Claims 1 and 11 above, and in further view of Kume et al (2000; *of record).

Response to Arguments

Applicant argues that Kume et al do not cure the defect of Havemann et al, Souttou et al and Powers et al.

Applicant's argument(s) has been fully considered, but is not persuasive. The Examiner's response to Applicant's argument(s) regarding Havemann et al, Souttou et al and Powers et al are discussed above and incorporated herein. Applicant does not contest the teachings of Kume et al as applied to the obviousness to substitute the retroviral expression vector by Havemann et al with a bicistronic retroviral expression vector as taught by Kume et al, with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

13. **Claim 4 stands rejected under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (*of record) in view of Souttou et al (2001; *of record in IDS), Powers et al (2002; *of record) and Kume et al (2000; *of record), as applied to Claims 1, 3 and 11 above, and in further view of Pufe et al (2003; *of record in IDS), Howett et al (*of record) and Eslami et al (2001; *of record).

Response to Arguments

Applicant argues that Pufe et al, Howett et al and Eslami et al do not cure the defect of Havemann et al, Souttou et al, Powers et al and Kume et al.

Applicant's argument(s) has been fully considered, but is not persuasive. The Examiner's response to Applicant's argument(s) regarding Havemann et al, Souttou et al, Powers et al and

Kume et al are discussed above and incorporated herein. Applicant does not contest the teachings of Pufe et al, Howett et al and Eslami et al as applied to the obviousness to substitute a first mononuclear/monocyte cell with a second monocyte cell, specifically THP-1, with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

14. **Claim 12 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (*of record) in view of Souttou et al (2001; *of record in IDS), Powers et al (2002; *of record), Kume et al (2000; *of record), Pufe et al (2003; *of record in IDS), Howett et al (*of record) and Eslami et al (2001; *of record), as applied to Claims 1, 3-4 and 11 above, and in further view of Kawamoto et al (Circulation 103:634-637, 2001).

Determining the scope and contents of the prior art.

Havemann et al do not teach the step of administering the genetically modified monocytes to a subject so that the transdifferentiation of said monocytes into endothelial cells occurs *in vivo*. However, at the time of the invention, Kawamoto et al taught the *in vivo* transplantation of endothelial progenitor cells obtained from mononuclear cells, whereby said transplanted endothelial progenitor cells differentiated into endothelial cells (Figure 1).

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute the *in vitro* transdifferentiation step as taught by Havemann et al with an *in vivo* transdifferentiation step, with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to substitute the *in vitro* transdifferentiation step with an *in vivo* transdifferentiation step because PTN has been repeatedly reported to induce the proliferation of endothelial cells and is an art-recognized angiogenic factor (Pufe) and Kawamoto et al successfully demonstrated the ability of monocytes to transdifferentiate into endothelial cells and incorporate at sites of neovascularization when implanted *in vivo*, thereby improving blood flow from an ischemic event.

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

15. **Claims 5 and 13 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (*of record) in view of Souttou et al (2001; *of record in IDS) and Powers et al (2002; *of record).

Determining the scope and contents of the prior art.

Havemann et al disclose endothelial cells obtained by a method comprising culturing mononuclear cells from the blood with a growth factor for endothelial cells, wherein the growth factor is pleiotrophin [0015, 0037]. The mononuclear cells include monocytes [0070]. The mononuclear cells are cultured for further differentiation and proliferation into endothelial precursor cells, developing surface markers increasingly typical of monocytes. These endothelial precursor cells can be isolated, proliferated further and differentiated to give endothelial cells [0069].

The mononuclear cells may be transformed *in vitro* with a gene encoding an effector gene, i.e. a growth factor, to promote the endothelialization of injured vessels or angiogenesis [0032, 0047, 0075, 0191], wherein the transgene may be unrestrictedly activatable, and activation of the activation sequence is self-enhancing [0042], and wherein the transgene is encoded by a viral vector [0049].

With respect to the steps of differentiating the monocytes into endothelial cells *in vitro*, Havemann et al disclose the isolated mononuclear cells are cultured and differentiated to give endothelial-like cells *in vitro* [0067, 0069].

Havemann et al do not disclose *ipsis verbis* that the viral vector to transfect the mononuclear cells to be a retroviral vector; however, Havemann et al disclose that the vector may be a viral vector [0049], and those of ordinary skill in the prior art recognized that retroviral vectors are used to express an active compound [0002, 0004]. Based on the teachings in the art

as a whole, one of ordinary skill in the art would have known that a retroviral vector could be used to transform a gene encoding a growth factor into the monocytic cells.

Havemann et al does not teach the pro-angiogenic effector transgene to encode PTN. However, at the time of the invention, Souttou et al taught that PTN is an angiogenic factor acting on endothelial cell proliferation, migration, survival, and capillary-like structure formation (pg 64, col. 1, last ¶).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in development and molecular and cellular biology. Therefore, the level of ordinary skill in this art is high.

"A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007). "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at ___, 82 USPQ2d at 1396.

The instantly claimed invention is predicated on the observation that monocytes differentiate into endothelial cells when stimulated by/exposed to PTN. However, the scientific concept that mononuclear cells [which includes monocytes] may differentiate into endothelial cells via stimulation by/exposure to PTN was previously taught by Havemann et al.

The instant claims require the endothelial cell progenitors to express PTN, thereby promoting differentiation into endothelial cells. However, the art recognized that PTN has autocrine and paracrine stimulatory activities in cells expressing both PTN and the PTN receptor (Powers et al, pg 14155, col. 1, ¶4). While Havemann et al do not teach *ipsis verbis* that the mononuclear cells/monocytes express the PTN receptor, those of ordinary skill in the art would

reasonably understand that the PTN receptor is necessarily present because the mononuclear cells/monocytes are disclosed to respond to PTN to give rise to endothelial cells. Thus, the expression of an effector transgene in the mononuclear cells [which includes monocytes] (Havemann) encoding PTN (Souttou) would be reasonably expected to achieve autocrine and paracrine stimulatory activities (Powers), promoting the differentiation of the mononuclear cells into endothelial cells (Havemann).

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to try substituting the transgene encoding a first pro-angiogenic growth factor as taught by Havemann et al with a transgene encoding a second pro-angiogenic growth factor, specifically the PTN growth factor as taught by Souttou et al, with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention and "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipate success, it is likely that product not of innovation but of ordinary skill and common sense." M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945) "Reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening in a jig-saw puzzle." 325 U.S. at 335, 65 USPQ at 301.)". When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. An artisan would be motivated to try substituting the transgene encoding a first pro-angiogenic growth factor growth factor for promoting angiogenesis with a transgene encoding a second pro-angiogenic growth factor, specifically the PTN growth factor, because Havemann et al disclose a finite number of identified, predictable potential solutions and Souttou et al teach that PTN is an angiogenic factor

acting on endothelial cell proliferation, migration, survival, and capillary-like structure formation.

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

16. **Claim 7 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (*of record) in view of Souttou et al (2001; *of record in IDS) and Powers et al (J2002; *of record), as applied to Claims 5 and 13 above, and in further view of Kume et al (2000; *of record).

Determining the scope and contents of the prior art.

Neither Havemann et al, Souttou et al nor Powers et al teach the retrovirus expression vector to be a bicistronic retrovirus. However, at the time of the invention, Kume et al taught the use of bicistronic retroviral vectors containing a marker gene, e.g. green fluorescent protein.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute the retroviral expression vector by Havemann et al with a bicistronic retroviral expression vector as taught by Kume et al, with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)" When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. An artisan would be motivated to substitute the retroviral expression vector by Havemann et al with a bicistronic retroviral expression vector, because Kume et al teach that the

bicistronic retroviral expression vector comprising a marker gene is a powerful tool for detailed analysis of transduced cells in conjunction with lineage differentiation, greatly facilitates developing and improving gene transfer strategies, as well as allowing the artisan to visualize transduced cells that have subsequently been transplanted into a host subject (Abstract; pgs 1196-1197, joining ¶).

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

17. **Claim 8 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (*of record) in view of Souttou et al (2001; *of record in IDS), Powers et al (2002; *of record) and Kume et al (2000; *of record), as applied to Claims 5, 7 and 13 above, and in further view of Pufe et al (2003; *of record in IDS), Howett et al (*of record) and Eslami et al (2001; *of record).

Determining the scope and contents of the prior art.

Neither Havemann et al, Souttou et al, Powers et al nor Kume et al teach the monocytes to be THP-1 monocytes. However, at the time of the invention, Pufe et al taught that THP-1 cells are responsive to PTN stimulation (pg 665, Figure 6).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

Applicant's intended use of the monocytes transfected with a nucleic acid encoding PTN, thereby inducing differentiation into endothelial cells comprises promoting neovascularization to treat diseases such as ischemia by enhancing or promoting the activity of PTN (pg 8, ¶3).

At the time of the invention, THP-1 monocyte cells were recognized in the art to be useful for implantation into a host subject (Howett et al; col. 17, Example 5) and capable of binding to injured human vein grafts (Eslami et al).

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute a first mononuclear/monocyte cell as taught by Havemann et al with a second monocyte cell, specifically THP-1 as taught by Pufe et al, with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)" When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. An artisan would be motivated to substitute a first mononuclear/monocyte cell with a second monocyte cell, specifically THP-1, because THP-1 cells are known in the art to be responsive to PTN (Pufe), adhere to injured vein grafts (Eslami), and thus the ordinary artisan has a reasonable expectation that THP-1 cells transfected with a transgene encoding PTN (Havemann, Souttou, Pufe) would adhere at sites of ischemia, thereby expressing the pro-angiogenic growth factor, PTN, and promote the endothelialization of injured vessels or angiogenesis (Havemann, Souttou).

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

18. **Claim 12 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (*of record) in view of Souttou et al (2001; *of record in IDS), Powers et al (2002; *of record), Kume et al (2000; *of record), Pufe et al (2003; *of record in IDS), Howett et al (*of record) and Eslami et al (2001; *of record), as applied to Claims 1, 3-4 and 11 above, and in further view of Kawamoto et al (Circulation 103:634-637, 2001).

Claim interpretation: to the extent that the claims are drawn to an isolated endothelial cell that transdifferentiated from a monocyte *in vivo*, and the specification discloses figures of isolated tissue comprising said endothelial cell that transdifferentiated from a monocyte *in vivo*

(Figures 5A-H), the Examiner interprets isolated tissue comprising endothelial cell(s) that transdifferentiated from a monocyte *in vivo* to fulfill the limitations of the claim.

Determining the scope and contents of the prior art.

Havemann et al do not teach the step of administering the genetically modified monocytes to a subject so that the transdifferentiation of said monocytes into endothelial cells occurs in vivo. However, at the time of the invention, Kawamoto et al taught the *in vivo* transplantation of endothelial progenitor cells obtained from mononuclear cells, and isolated tissue comprising endothelial cells that had transdifferentiated from said mononuclear cells *in vivo* (Figures 1 and 2).

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute the *in vitro* transdifferentiation step as taught by Havemann et al with an *in vivo* transdifferentiation step, with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to the *in vitro* transdifferentiation step with an *in vivo* transdifferentiation step because PTN has been repeatedly reported to induce the proliferation of endothelial cells and is an art-recognized angiogenic factor (Pufe) and Kawamoto et al successfully demonstrated the ability of monocytes to transdifferentiate into endothelial cells and incorporate at sites of neovascularization when implanted *in vivo*, thereby improving blood flow from an ischemic event.

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Conclusion

19. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to KEVIN K. HILL whose telephone number is (571)272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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